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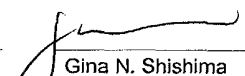
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July 2, 2003

CERTIFICATE OF MAILING 37 C.F.R. 1.8	
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Date	Gina N. Shishima

**MS DD**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

RE: *U.S. Patent Application No. 10/057,834 entitled "COMPOSITIONS AND METHODS FOR OPTIMIZING UGT2B7 SUBSTRATE DOSINGS AND FOR PREDICTING UGT2B7 SUBSTRATE TOXICITY" – Mark J. Ratain et al.*  
*Our reference: ARCD:358US*  
*Client reference: UCHI:846*

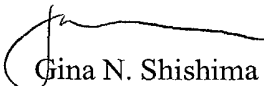
Sir:

Enclosed for filing in the above-referenced patent application is a Supplemental Information Disclosure Statement, Form PTO-1449, and references A2, B2-B5, C29-C195.

No fees are believed to be due in connection with the filing of this Supplemental Information Disclosure Statement, however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary for any reason relating to the enclosed materials, the Commissioner is authorized to deduct the appropriate fees from Fulbright & Jaworski Deposit Account No.: 50-1212/ARCD:358US.

Please date stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

  
Gina N. Shishima  
Reg. No. 45,104

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:  
Mark J. Ratain *et al.*

Serial No.: 10/057,834

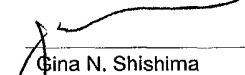
Filed: January 25, 2002

For: COMPOSITIONS AND METHODS FOR  
OPTIMIZING UGT2B7 SUBSTRATE  
DOSINGS AND FOR PREDICTING  
UGT2B7 SUBSTRATE TOXICITY

Group Art Unit: 1645

Examiner: Unknown

Atty. Dkt. No.: ARCD:358US

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July 2, 2003	
Date	Gina N. Shishima

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

**MS DD**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Supplemental Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are enclosed for the convenience of the Examiner.

In accordance with 37 C.F.R §§ 1.97(g), (h), this Supplemental Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be

construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

The present Supplemental Information Disclosure Statement is being filed prior to the receipt of a first Official Action reflecting an examination on the merits, and hence is believed to be timely filed in accordance with 37 C.F.R. § 1.97(b). No fees are believed to be due in connection with the filing of this Supplemental Information Disclosure Statement, however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary for any reason relating to these materials, the Commissioner is authorized to deduct the appropriate fees from Fulbright & Jaworski Deposit Account No.: 50-1212/ARCD:358US.

The above mentioned application is related by subject matter and/or by inventors to the following U.S. patent application serial numbers: 08/423,641 now issued as patent no. 5,786,344, 08/271,278, 09/553,829, 09/251,274 now issued as patent no. 6,395,481, 10/061,693 now issued as patent no. 6,472,157, 10/277,160, 09/835,082, and provisional application serial numbers 60/437,928 and 60/446,942.

Applicants respectfully request that the listed documents be made of record in the present case.

Respectfully submitted,



Gina N. Shishima  
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Attorney for Applicants

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List of Patents and Publications for Applicant's

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INFORMATION DISCLOSURE STATEMENT

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### U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.
	A2	6,066,645	5/23/00	Hausheer <i>et al.</i>	514	283	1/6/99

### Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Class	Sub Class	Translation Yes/No
	B2	EP 0919244	6/2/99	Europe			Abstract
	B3	WO 94/22846	10/94	PCT			
	B4	WO 95/08986	4/6/95	PCT			
	B5	WO 96/01127	1/18/96	PCT			

### Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C29	Abraham <i>et al.</i> , "Non-glucocorticoid steroid analogues (21-aminosteroids) sensitize multidrug resistant cells to vinblastine," <i>Cancer Chemother. Pharmacol.</i> , 32(2):116-122, 1993.
	C30	Akiyama <i>et al.</i> , "Most drugs that reverse multidrug resistance also inhibit photoaffinity labeling of p-glycoprotein by a vinblastine analog," <i>Mol. Pharmacol.</i> , 33(2):144-147, 1988.
	C31	Ansher <i>et al.</i> , "Chemoprotective effects of two dithiolthiones and of butylhydroxyanisole against carbon tetrachloride and acetaminophen toxicity," <i>Hepatology</i> , 3(6):932-935, 1983.
	C32	Araki <i>et al.</i> , "Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and blood plasma of athymic mice following intraperitoneal administration of CPT-11," <i>Jpn J. Cancer Res.</i> , 84:697-702, 1993.
	C33	Ariyoshi <i>et al.</i> , "Mouse-human chimeric antibody MH171 against the multidrug transporter P-glycoprotein," <i>Jpn. J. Cancer Res.</i> , 83(5):515-521, 1992.
	C34	Atsumi <i>et al.</i> , "Identification of the Metabolites of Irinotecan, a New Derivative of Camptothecin, in Rat Bile and its Biliary Excretion," <i>Xenobiotica</i> , 21(9):1159-1169, 1991.
	C35	Bear, "Drugs transported by-P-glycoprotein inhibit a 40pS outwardly rectifying chloride channel," <i>Biochem. Biophys. Res. Commun.</i> , 200(1):513-521, 1994.

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## Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C36	Bell <i>et al.</i> , "Roles of peptidyl-prolyl cis-trans isomerase and calcineurin in the mechanisms of antimalarial action of cyclosporin A, FK506, and rapamycin," <i>Biochem. Pharmacol.</i> , 48(3):495-503, 1994.
	C37	Bertrand <i>et al.</i> , "Sequential Administration of Camptothecin and Etoposide Circumvents the Antagonistic Cytotoxicity of Simultaneous Drug Administration in Slowly Growing Human Colon Carcinoma HT-29 Cells," <i>Eur. J. Cancer</i> , 28A(4-5):743-748, 1992.
	C38	Beutler <i>et al.</i> , "Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism," <i>PNAS USA</i> , 95:8170-8174, 1998.
	C39	Bible and Kaufmann, "Cytotoxic synergy between flavopiridol (NSSC 649890, L86-8275) and various antineoplastic agents: the importance of sequence of administration," <i>Cancer Res.</i> , 57:3375-3380, 1997.
	C40	Bible and Kaufmann, "Flavopiridol: a cytotoxic flavone that induces cell death in noncycling A549 human lung carcinoma cells," <i>Cancer Res.</i> , 56:4856-4861, 1996.
	C41	Bock <i>et al.</i> , In: <i>Conjugation reactions in biotransformation</i> , Elsevier, North Holland Biomedical Press, p. 357-364, 1978.
	C42	Boesch and Loor, "Extent and persistence of P-glycoprotein inhibition in multidrug-resistant P388 cells after exposure to resistance-modifying agents," <i>Anticancer Drugs</i> , 5(2):229-238, 1994.
	C43	Boesch <i>et al.</i> , "Restoration of daunomycin retention in multidrug-resistant P388 cells by submicromolar concentrations of SDZ PSC 833, a nonimmunosuppressive cyclosporin derivative," <i>Exp. Cell. Res.</i> , 196(1):26-32, 1991.
	C44	Boiteux-Antoine <i>et al.</i> , "Comparative induction of drug-metabolizing enzymes by hypolipidaemic compounds," <i>Gen-Pharmacol</i> , 20(4):407-412, 1989.
	C45	Bosma <i>et al.</i> , "Sequence of exons and the flanking regions of human bilirubin-UDP-glucuronosyltransferase gene complex and identification of a genetic mutation in a patient with Crigler-Najjar Syndrome, Type I," <i>Hepatology</i> , 15:941-947, 1992.
	C46	Bosma <i>et al.</i> , "The genetic basis of the reduced expression of bilirubin UDP-Glucuronosyltransferase 1 in Gilbert's Syndrome," <i>N. Eng. J. Med.</i> , 333:1171-1175, 1995.
	C47	Burchell and Coughtrie, "UDP-glucuronosyltransferases," <i>Pharmac. Ther.</i> , 43:261-289, 1989.

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	C48	Burchell <i>et al.</i> , "The UDP Glucuronosyltransferase gene suprefamily: suggested nomenclature based on evolutionary divergence, <i>DNA cell biol.</i> , 10:487-494, 1991.
	C49	Burger <i>et al.</i> , "Pharmacokinetic interaction between rifampin and zidovudine," <i>Antimicrobial Agents and Chemotherapy</i> , 37(7):1426-1431, 1993.
	C50	Campain <i>et al.</i> , "Characterization of an unusual mutant of human melanoma cells resistant to anticancer drugs that inhibit topoisomerase II," <i>J. Cell Physiol.</i> , 155(2):414-425, 1993.
	C51	Carlson <i>et al.</i> , "Flavopiridol induces G <sup>1</sup> arrest with inhibition of cyclin-dependent kinase (CDK) 2 and CDK4 in human breast carcinoma cells," <i>Cancer Res</i> , 56:2973-2978, 1996.
	C52	Cascorbi <i>et al.</i> , "Frequency of single nucleotide polymorphisms in the p-glycoprotein drug transporter MDR1 gene in white subjects," <i>Clinic. Pharmacol Ther.</i> , 69:169-174, 2001.
	C53	Charuk <i>et al.</i> , "Interaction of Rat Kidney P-Glycoprotein with a Urinary Component and Various Drugs Including Cyclosporin A," <i>Am. J. Physiol.</i> , 266:F66-F75, 1994.
	C54	Chen <i>et al.</i> , "Calcium phosphate-mediated gene transfer: A highly efficient transfection system for stably transforming cells with plasmid DNA," <i>Biotechniques</i> , 6:632-638, 1988.
	C55	Chien <i>et al.</i> , "In vitro evaluation of flavopiridol, a novel cell cycle inhibitor, in bladder cancer," <i>Cancer Chemother Pharmacol</i> , 44:81-87, 1999.
	C56	Chin <i>et al.</i> , "Reduced mRNA levels for multidrug-resistance genes in cAMP-dependent protein kinase mutant cell lines," <i>J. Cell Physiol.</i> , 152(1):87-94, 1992.
	C57	Clarke <i>et al.</i> , "The Uridine Diphosphate glucuronosyltransferase multigene family: function and regulation," <i>Handbook of experimental pharmacology</i> , 112:3-43, 1994.
	C58	Coffman <i>et al.</i> , "Cloning and stable expression of a cDNA encoding a rat liver UDP-Glucuronosyltransferase (UDP-Glucuronosyltransferase 1.1) that catalyzes the glucuronidation of opioids and bilirubin," <i>Mol. Pharmacol.</i> , 47:1101-1105, 1995.
	C59	Cordon-Cardo <i>et al.</i> , "Expression of the multidrug resistant gene product (P-glycoprotein) in human normal and tumor tissues," <i>J. Histochem. Cytochem.</i> , 38:1277-1287, 1990.
	C60	Czech <i>et al.</i> , "Antitumoral activity of flavone L86-8275," <i>Int J Oncol</i> , 6:31-66, 1995.
	C61	Davies and Schnell, "Oltipraz-induced amelioration of acetaminophen hepatotoxicity in hamsters," <i>Toxicology and Applied Pharmacology</i> , 109:29-40, 1991.

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	C62	de Forni <i>et al.</i> , "Phase I and pharmacokinetic study of the camptothecin derivative irinotecan administered on a weekly schedule in cancer patients," <i>Cancer Res.</i> , 54:4347-4354, 1994.
	C63	De Lannoy <i>et al.</i> , "Cyclosporin and Quinidine Inhibition of Renal Digoxin Excretion: Evidence for Luminal Secretion of Digoxin," <i>Am. J. Physiol.</i> , 263:F613-F622, 1992.
	C64	De Moraes <i>et al.</i> , "Biotransformation and Toxicity of Acetaminophen in Congenic RHA Rats with or without a Hereditary Deficiency in Bilirubin UDP-Glucuronosyltransferase," <i>Toxicology and Applied Pharmacology</i> , 117:81-87, 1992.
	C65	Decleves <i>et al.</i> , "A new polymorphism (N21D) in the exon 2 of the human MDR1 gene encoding the P-glycoprotein," <i>Human Mutation</i> , 15: 486, 2000.
	C66	Dhainaut <i>et al.</i> , "New Triazine Derivatives as Potent Modulators of Multidrug Resistance," <i>J. Med. Chem.</i> , 35:2481-2496, 1992.
	C67	Di Carlo <i>et al.</i> , "Flavonoids: old and new aspects of a class of natural therapeutic drugs," <i>Life Sci</i> , 65:337-353, 1999.
	C68	Di Rienzo <i>et al.</i> , "Two new alleles in the promoter of the bilirubin UDP-glucuronosyl transferase 1 (UGT1A1) gene", <i>American Society for Clinical Pharmacology and Therapeutics</i> , Ninety Ninth Annual Meeting, New Orleans, Abstract OII-B-3, page 207, 1998.
	C69	Diasio <i>et al.</i> , "Clinical pharmacology of 5-fluorouracil," <i>Clin Pharmacokinet</i> , 16:215-237, 1989.
	C70	Doige <i>et al.</i> , "ATPase activity of partially purified P-glycoprotein from multidrug-resistant chinese hamster ovary cells," <i>Biochim. Biophys. Acta.</i> , 1109(2):149-160, 1992.
	C71	Drees <i>et al.</i> , "Flavopiridol (86-8275): selective antitumor activity in vitro and activity in vivo for prostate carcinoma cells," <i>Clin Cancer Res</i> , 3:273-279, 1997.
	C72	Egner <i>et al.</i> , "Regulation of Phase 2 Enzyme Induction by Oltipraz and other Dithiolethiones," <i>Carcinogenesis</i> , 15(2):177-181, 1994.
	C73	Ford <i>et al.</i> , "Cellular and biochemical characterization of thioxanthenes for reversal of multidrug resistance in human and murine cell lines," <i>Cancer Res.</i> , 50(6):1748-1756, 1990.
	C74	Fournel <i>et al.</i> , "Structure-dependent induction of bilirubin glucuronidation and lauric acid 12-hydroxylation by arylcarboxylic acids chemically related to clofibrate," <i>Biochimica et Biophysica Acta</i> , 842:202-213, 1985.

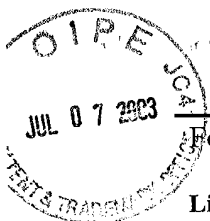
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## Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

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	C75	Foxwell <i>et al.</i> , "Identification of the multidrug resistance-related P-glycoprotein as a cyclosporine binding protein," <i>Mol. Pharmacol.</i> , 36:543-546, 1989.
	C76	Friche <i>et al.</i> , "In vitro circumvention of anthracycline-resistance in ehrlich ascites tumour by anthracycline analogues" <i>Biochem. Pharmacol.</i> , 39:1721-1726, 1990.
	C77	Gram <i>et al.</i> , "Clinical relevance of genetic polymorphisms in drug oxidation," <i>Clinical Relevance of Genetic Polymorphisms in Drug Oxidation</i> , 1992.
	C78	Green <i>et al.</i> , "Expressed human UGT1.4 protein catalyzes the formation of quaternary ammonium-linked glucuronides," <i>Drug Metab. Dispos.</i> , 23:299-302, 1995.
	C79	Gruol <i>et al.</i> , "Reversal of multidrug resistance by RU 486 <sup>1</sup> " <i>Cancer Res.</i> , 54(12):3088-3091, 1994.
	C80	Gunn, "Hereditary Acholuric Jaundice," <i>J. Hered.</i> , 29:137-139, 1938.
	C81	Gupta <i>et al.</i> , "Metabolic Fate of Irinotecan in humans: Correlation of Glucuronidation with Diarrhea," <i>Cancer Res.</i> , 54:3723-3725, 1994.
	C82	Gupta <i>et al.</i> , "Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor Irinotecan in cancer patients," <i>J. Clin. Oncol.</i> , 15:1502-1510, 1997.
	C83	Gupta <i>et al.</i> , "Role of carboxyl esterase in the metabolism of CPT-11, a camptothecin analog, in humans" <i>Pharm. Res.</i> , 11:S450, 1994.
	C84	Gutmann <i>et al.</i> , "Modulation of multidrug resistance protein expression in porcine brain capillary endothelial cells in vitro," <i>Drug Metab Dispos.</i> 27:937-941, 1999.
	C85	Hait <i>et al.</i> , "Terferadine (seldane®): a new drug for restoring sensitivity to multidrug resistant cancer cells" <i>Biochem. Pharmacol.</i> , 45(2):401-406, 1993.
	C86	Hamada <i>et al.</i> , "Mouse-human chimeric antibody against the multidrug transporter P-glycoprotein" <i>Cancer Res.</i> , 50(11):3167-3171, 1990.
	C87	Harding <i>et al.</i> , "Cloning and substrate specificity of a human phenol UDP-glucuronosyltransferase expressed in COS-7 cells," <i>PNAS, USA</i> , 85:8381-8385, 1988.
	C88	Hecht <i>et al.</i> , "4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide, metabolites of a tobacco-specific lung carcinogen, in the urine of black and white smokers," <i>Proceedings of the American Association for Cancer Research</i> , 35:1702, 1994.

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Form PTO-1449 (modified)		Atty. Docket No. ARCD:358US	Serial No. 10/057,834
List of Patents and Publications for Applicant's  INFORMATION DISCLOSURE STATEMENT  (Use several sheets if necessary)		Applicant Mark J. Ratain <i>et al.</i>	
		Filing Date: January 25, 2002	
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**Other Art (Including Author, Title, Date Pertinent Pages, Etc.)**

Exam. Init.	Ref. Des.	Citation
	C89	Hendricks <i>et al.</i> , "Effect of P-Glycoprotein Expression on the Accumulation and Cytotoxicity of Topotecan (SK&F 104864), a New Camptothecin Analogue," <i>Cancer Research</i> , 52:2268-2278, April 1992.
	C90	Hjelle, "Hepatic UDP-Glucuronic Acid Regulation during Acetaminophen Biotransformation in Rats," <i>The Journal of Pharmacology and Experimental Therapeutics</i> , 237(3):750-756, 1986.
	C91	Hoffmeyer <i>et al.</i> , "Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations an dcorrelation of one allele with p-glycoprotein expression and activity in vivo," <i>PNAS</i> , 28:97(7):3473-3478, 2000.
	C92	Hooijberg <i>et al.</i> , "Potent interaction of flavopiridol with MRP1," <i>British J. of Cancer</i> , 81:269-276, 1999.
	C93	Hunter <i>et al.</i> , "Drug absorption limited by P-glycoprotein-mediated secretory drug transport in human intestinal epithelial caco-2 cell layers" <i>Pharm. Res.</i> , 10(5):743-749, 1993.
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Applicant  
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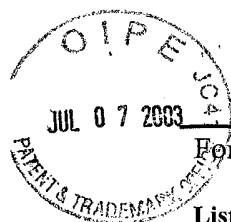
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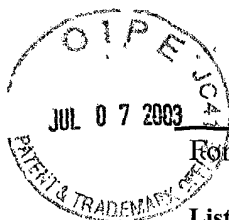
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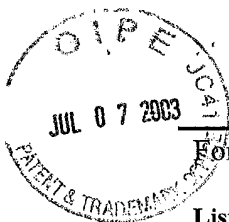
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List of Patents and Publications for Applicant's  INFORMATION DISCLOSURE STATEMENT  (Use several sheets if necessary)		Applicant Mark J. Ratain <i>et al.</i>	
		Filing Date: January 25, 2002	Group: 1645
U.S. Patent Documents <i>See Page 1</i>	Foreign Patent Documents <i>See Page 1</i>	Other Art <i>See Page 1</i>	

**Other Art (Including Author, Title, Date Pertinent Pages, Etc.)**

Exam. Init.	Ref. Des.	Citation
	C188	Tucker, "Clinical implications of genetic polymorphism in drug metabolism," <i>J. Pharm. Pharmacology</i> , 46:417-424, 1994.,
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